PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Inventor: | Castillo et al. | Examiner: | Jiang, S. |
| Serial No.: | 10/099,637 | Group Art Unit: | 1617 |
| Filing Date: | 3/15/2002 | Attorney Docket No.: | PROTEO.P16CI |

Title of Invention: Catechins for the Treatment of Fibrillogenesis in Alzheimer's Disease, Parkinson's Disease, Systemic AA Amyloidosis, and Other Amyloid Disorders

Seattle, Washington 98109
July 11, 2003

TO THE COMMISSIONER FOR PATENTS
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. ALAN D. SNOW UNDER RULE 132

Alan D. Snow declares:

1. I am over the age of 18, and competent to testify in this matter. I am a co-inventor of the above invention.

2. I read the Examiner's latest office action mailed January 28, 2003 to imply that Aß nerve cell toxicity NECESSARILY (that is, 'inherently') teaches an effect on inhibition of Aß fibril formation, deposition, accumulation and/or persistence. I do not believe the literature supports such an implication, for reasons as detailed further herein.

3. At least one study by Wang (Wang, The Neuroprotective Effects of Phytoestrogens on Amyloid ß Protein-induced Toxicity Are Mediated by Abrogating the Activation of Caspase Cascade in Rat Cortical Neurons, J. Biological Chem., vol 276 no 7, pp 5287-5295, February 16, 2001) (copy attached for Examiner's ready reference) reports that "although Aß mediated neurotoxicity [is a] focus of intense interest, the underlying mechanisms are still controversial"

(see p 5294, col 2 below fig. 9). Thus, there can be no necessary inference to be drawn from any study of Aß mediated neurotoxicity.

4. Wang also reports that nerve cell death or neurotoxicity is in fact the result of a cascade involving caspases and reactive oxygen species accumulation (see abstract p 5287 - near end). Also, Zhang (Zhang, Selective Cytotoxicity of Intracellular Amyloid ß Peptide 1-42 Through p53 and Bax in Cultured Primary Human Neurons, J. Cell Bio., vol 156 no 3, pp 519-529, February 3, 2002) (copy attached for Examiner's ready reference) reports that nonfibrilized and fibrilized Aß are equally toxic (see p 519, midway thru abstract), and corroborates Wang in suggesting a caspase cell death route (see p 525, col 1, 1st paragraph). This is further refutation that there is no necessary suggestion from any study that inhibition of Aß neurotoxicity will also lead to inhibition of Aß fibril formation, deposition, accumulation and/or persistence. There is likewise no suggestion in any of the literature that fibrillogenesis plays any part whatever in the reported cell death.

5. Wang even reports that the high antioxidant activity of flavanoids *per se* was not able to protect neurons against Aß-induced neurotoxicity (see p 5292, col 1, end of penultimate paragraph); thus teaching away from a suggestion that flavanoids might be useful in preventing Aß fibrillogenesis.

6. Thus there are no necessary inferences available as teachings to be applied to Aß fibrillogenesis from the cited studies pertaining to neuronal cell death, because in at least some of the reported studies, the causes of the cell death do not involve any effect on Aß fibrillogenesis. There is thus no implication available to serve as a teaching that inhibition of nerve cell death or nerve cell toxicity by Aß inherently leads to inhibition of Aß fibril formation, deposition, accumulation and/or persistence.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the accompanying application or any patent issued thereon.

DATED July 11, 2003

DR. ALAN D. SNOW